Structural fine-tuning in the chemistry of frustrated Lewis pairs

Summary of PhD dissertation

Éva Dorkó

Eötvös Loránd University, Faculty of Science
Doctoral School of Chemistry
Head of School: *Dr. Attila Császár*

Synthetic Chemistry, Material Science and Biomolecular Chemistry
Head of Program: *Dr. András Perczel*

Hungarian Academy of Sciences, Research Centre for Natural Sciences
Institute of Organic Chemistry

Supervisor: *Dr. Tibor Soós*
Head of Institute

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1. Intoduction

Most of the chemical transformations implemented by the food industry, the chemical industry and the pharmaceutical industry are catalytic process, therefore catalysts plays an important role in maintaining modern lifestyle. One of the most important reactions is catalytic hydrogenation, where usually transition metals are used but the toxicity problems and the tightening purity requirements concerning the product arisen the need for producing non-transition metal hydrogenation catalysts.

The principle of the frustrated Lewis pairs (FLP), which was first published by Stephan and his colleagues in 2006,[1] provides a new strategy in the development of catalytic systems based on main group elements. The FLP system, which contains a sterically hindered Lewis acid and a Lewis base is able to split the hydrogen molecule heterolytically and reduce various activated double bonds without using transition metals.[2]

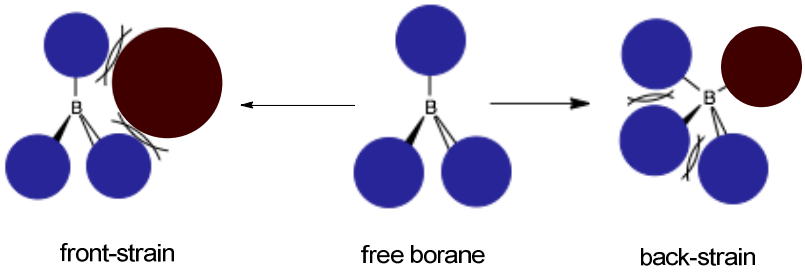
Despite the results provided by the researches concerning FLP catalysis in the last decades, a number of disadvantages still require further development. Presently, the biggest known disadvantage of the FLP systems is that they are applicable only under inert conditions with special equipment, since they are sensitive to the presence of water.

One of the main trends in our research group is the synthesis and application of FLP catalysts. During my PhD studies I used the previous observations, and worked on developing new frustrated FLP catalysts which can tolerate water and can be used without requiring inert conditions in catalytic hydrogenations, even in reactions which results in the emergence of large amount of water. I aimed for achieving water tolerance by fine-tuning the structure of the Lewis acid and Lewis bases used in the catalysis. The optimisation of the structure of the catalysts is a complex task, as the reactivity of the catalyst is heavily influenced by the strength of the Lewis acid and Lewis base. Therefore I also aimed for analysing and separating the effects influencing the Lewis acidity and basicity strength and for examining their influence on the catalytic reactivity of the employed FLP systems used during the experiments. These observations made the fine-tuning of the ELP catalyst possible, and the reductive amination of carbonyl compounds was achieved.

2. Aims of the Present Work

One of the most significant hardships of synthetizing new Lewis acids (LA) is evaluating their strength. Consequently finding a method to separate and understand the effect of the structural parameters to the Lewis acidity and to the chemical reactivity is a vital part of catalyst development. The purposive and methodical development of the catalysts in the future can be made possible by the examination, quantification and fine-tuning of the electronic and steric – both front- and back-strain – effects.

The electron density of the boron is influenced by the electronic factors; the electron donating and -withdrawing groups on the aryl rings of the boron centre. The steric factors affect the accessibility of the boron centre, which depends on the size of the ligands attached to the boron. Two kind of steric effect can be separated, which can either prevent or destabilise the forming dative bond during the reaction of a Lewis acid and a base, because of the van der Waals repulsion of the huge ligands (Scheme 1.).

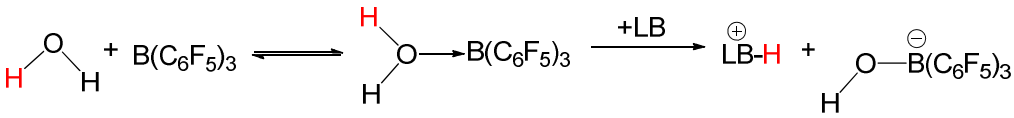


Scheme 1. Steric effects. Blue balls: ligands of the triaryl-borane. Brown balls: coordinating base

A large base coordinating to the Lewis acid may cause *front-strain*, the repulsion between the ligands of the acid and the base. *Back-stain* effect may occurs, if repulsion between the ligands of the acid inhibits the change of the structure during the formation of a dative bond.

We aimed for examining the acidity strength of the triaryl-borane type Lewis acids and to separate the effects influencing them. We wished to study whether the different effects can be modified independently and how they influence the chemical reactivity of the catalyst. The question was also arisen, how the front- and back-strain alters, if we change the most common triaryl-boranes, which are symmetrically substituted in the *orto*-position, to non-symmetrically substituted boranes. We also aimed for the examination of water tolerance.

According to the literature, the reduction of nitrogen containing compounds in the presence of water is not solved yet, because the LA-OH_2 adduct emerging is highly acidic, and can be deprotonated by the strong Lewis base (Scheme 2.).



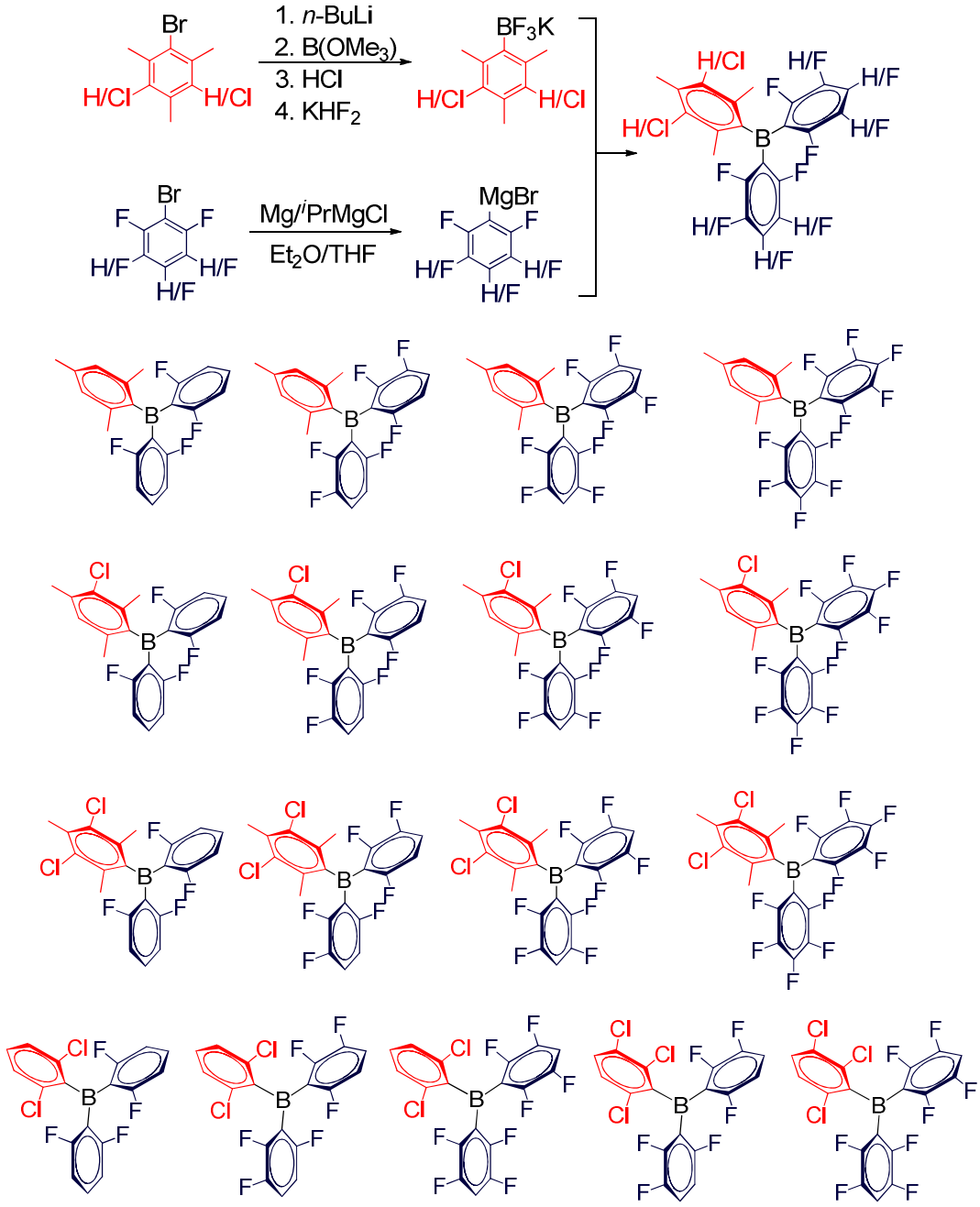
Scheme 2. Decomposition of triaryl boranes

We assumed that the dative bond between the Lewis acid and water can be weaken by separating the steric parameters and by fine-tuning the Lewis acid, and the forming equilibrium can be shifted toward the free borane. Therefore we planned to synthesize Lewis acids, with which the forming LS-OH_2 adduct cannot be deprotonated in the presence of a strong nitrogen base.

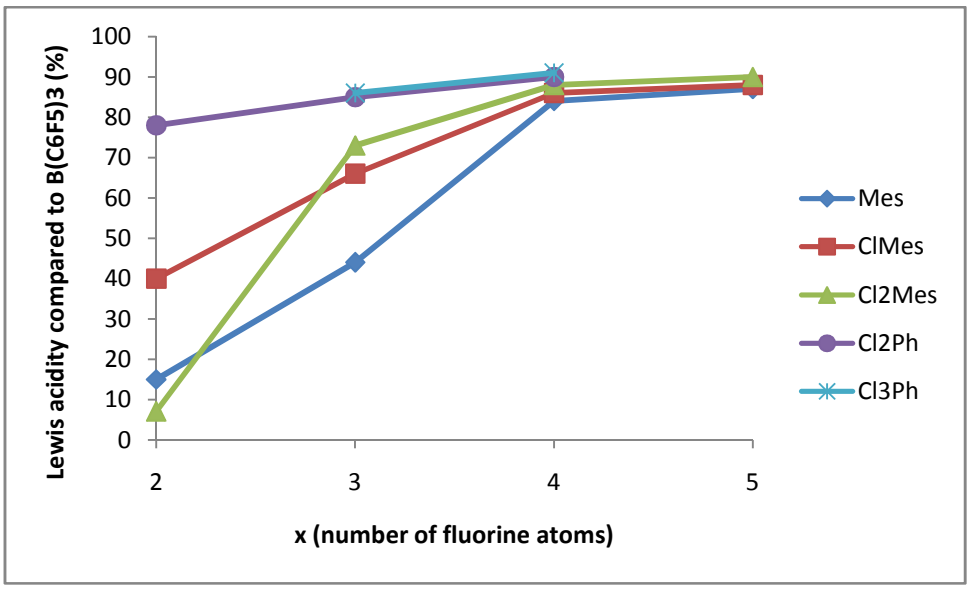
3. Results

The results of my research can be summarized in the following points:

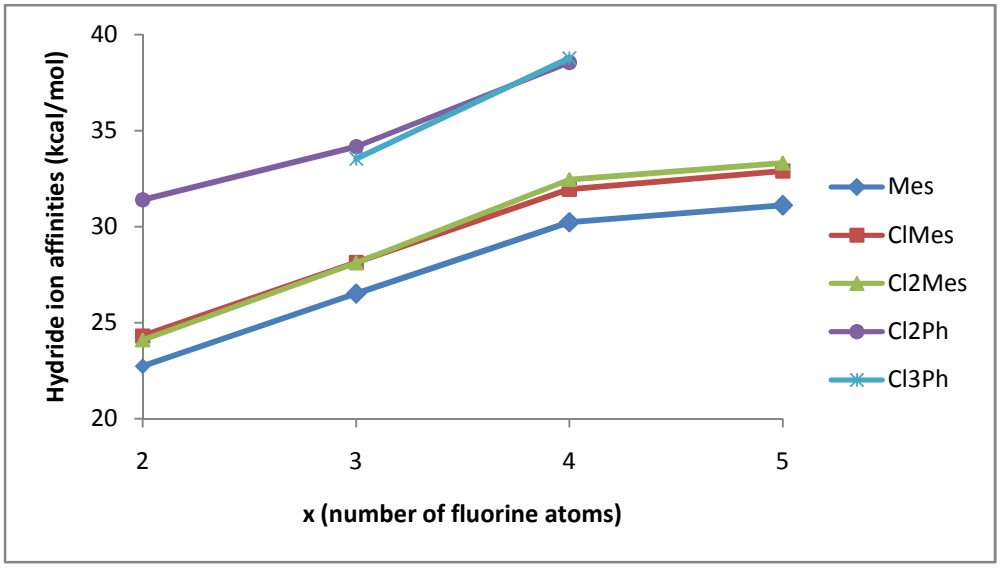
1. During our experiments we synthesized seventeen BX_2Y boranes, by exchanging H atoms in *meta*- and *para*-positions with chlorine and fluorine atoms to have their steric properties similar but to change their electronic properties.



2. The Lewis acidity of the synthesized boranes was measured using the Gutmann-Beckett method (Scheme 3.), and the hydride ion affinities were calculated by theoretical methods (Scheme 4.)

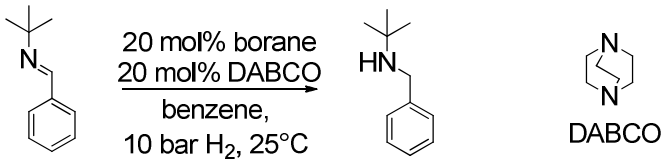


Scheme 3. Relative Lewis acidity of $B(C_6F_xH_{5-x})_2Y$ *via* Gutmann-Beckett method, where x is the number of fluorines on the two equivalent phenyl rings and Y is the third ring (mesityl- (**Mes**), 3-chloromesityl- (**ClMes**), 3,5-dichloromesityl (**Cl_2Mes**), 2,6-dichlorophenyl- (**Cl_2Ph**), 2,3,6-trichlorophenyl ring (**Cl_2Ph**)).

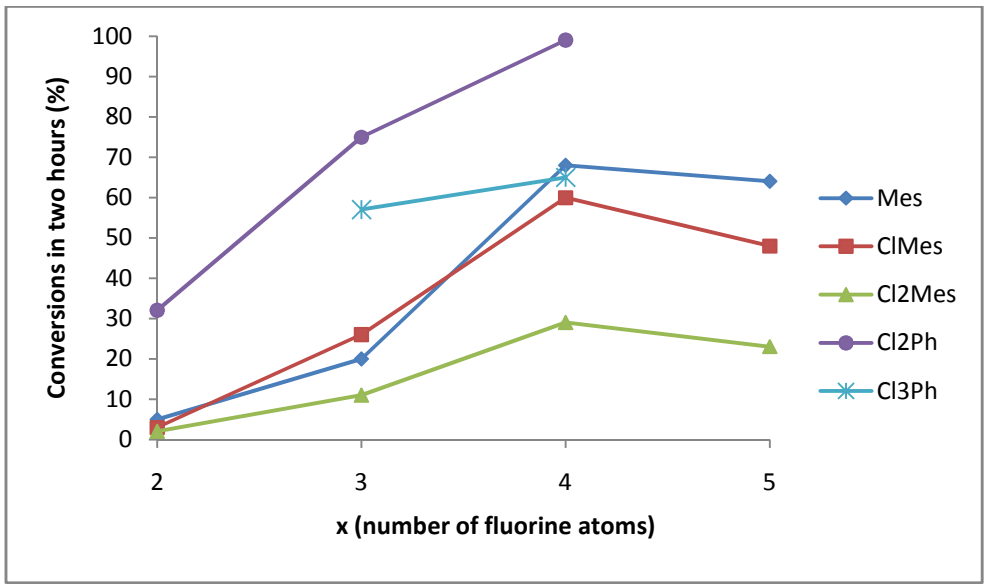


Scheme 4. *Hydride ion affinity* of $B(C_6F_xH_{5-x})_2Y$ boranes where x is the number of fluorines on the two equivalent phenyl rings and Y is the third ring (mesityl- (**Mes**), 3-chloromesityl- (**ClMes**), 3,5-dichloromesityl (**Cl_2Mes**), 2,6-dichlorophenyl- (**Cl_2Ph**), 2,3,6-trichlorophenyl ring (**Cl_2Ph**)).

3. The chemical reactivity of the produced boranes was tested during the reduction of *tert*-butyl-benzaldimine (Scheme 5.). Due to the conversions (Scheme 6.), all boranes were effective catalysts with DABCO as co-catalyst. The boranes with chlorophenyl rings were more efficient, than the ones with mesityl rings. It was observed that in case of sterically hindered boranes, the Gutmann-Becket method is inapt to have connection established between acidity strength and capacity of hydrogenation. But the calculated hydride ion affinity rate is suitable to estimate Lewis acidity and reactivity.



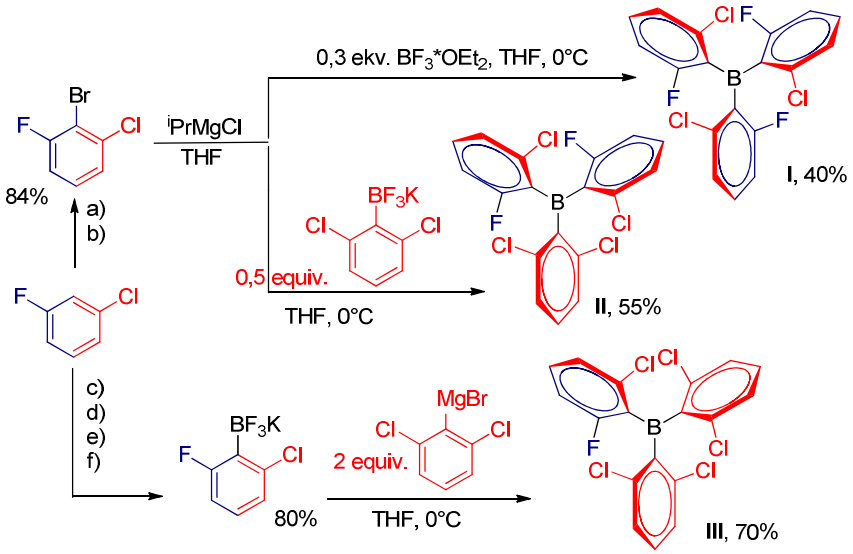
Scheme 5. Reduction of *tert*-buthl-benzaldimine with $B(C_6F_xH_{5-x})_2Y$ as catalyst



Scheme 6. *Conversions* in two hours with $B(C_6F_xH_{5-x})_2Y$ as catalyst, where x is the number of fluorines on the two equivalent phenyl rings and Y is the third ring (mesityl- (**Mes**), 3-chloromesityl- (**ClMes**), 3,5-dichloromesityl (**Cl_2Mes**), 2,6-dichlorophenyl- (**Cl_2Ph**), 2,3,6-trichlorophenyl ring (**Cl_2Ph**)).

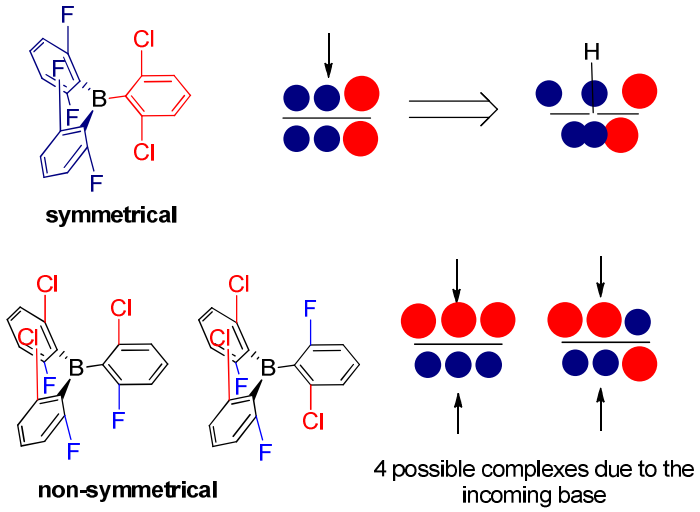
4. As a general principle the H/F exchange in *meta*-position increases Lewis acidity, however the H/Cl exchange on a sterically hindered aromatic ring has negligible effect. This information can be useful in the development of other FLP catalysts.

5. During our examinations, non-symmetrical triaryl-boranes were synthesized (Scheme 7.).



Scheme 7. Conditions: a) 1,1 equiv. BuLi, THF; b) 1,5 equiv. Br_2; c) 1,1 equiv. BuLi, THF, -78°C; d) 2 equiv. $B(OMe)_3$; e) 1,4 equiv. 1M HCl, 0°C; f) 4 equiv. KHF_2 in $MeOH/H_2O$

6. The non-symmetrically substituted boranes have variable acidity strength. Due to their unique structure, the incoming base can sense different environments because of the differences between the ligands positioned below and above a plain defined by the boron and the aromatic rings (Scheme 8.).



Scheme 8. The concept of variable Lewis acidity. Red dots: Chlorine atoms. Blue dots: fluorine atoms. The black line presents the plain defined by the boron and the aromatic rings.

7. The hydride ion affinity and the Lewis acidity of the non-symmetrically substituted boranes were determined by the Gutmann-Beckett method, while their reduction potential was determined by cyclic voltammetry (Table 1.). According to the hydride ion affinity, borane **III** has the greatest back strain; and the cyclic voltammetry shows that it is the most electron deficient. According to the Gutmann-Beckett method, borane I is the most acidic, because of the growing steric strain.

	Method	I	II	III
1	Hydride ion affinity[a]	32,3	30,9	29,8
2	Cyclic voltammetry[b]	-2,1	-2,0	-1,9
3	Gutmann-Beckett[c]	77	5	4

Table 1. The measurement of Lewis acidity. [a] The hydride ion affinity of the most stable conformations, kcal/mol. [b] The reduction potentials measured by cyclic voltammetry (V). [c] Relative %; the 0% and 100% reference points are the ^{31}P NMR chemical shift of $Et_3P{=}O$ and it's adduct with $B(C_6F_5)_3$

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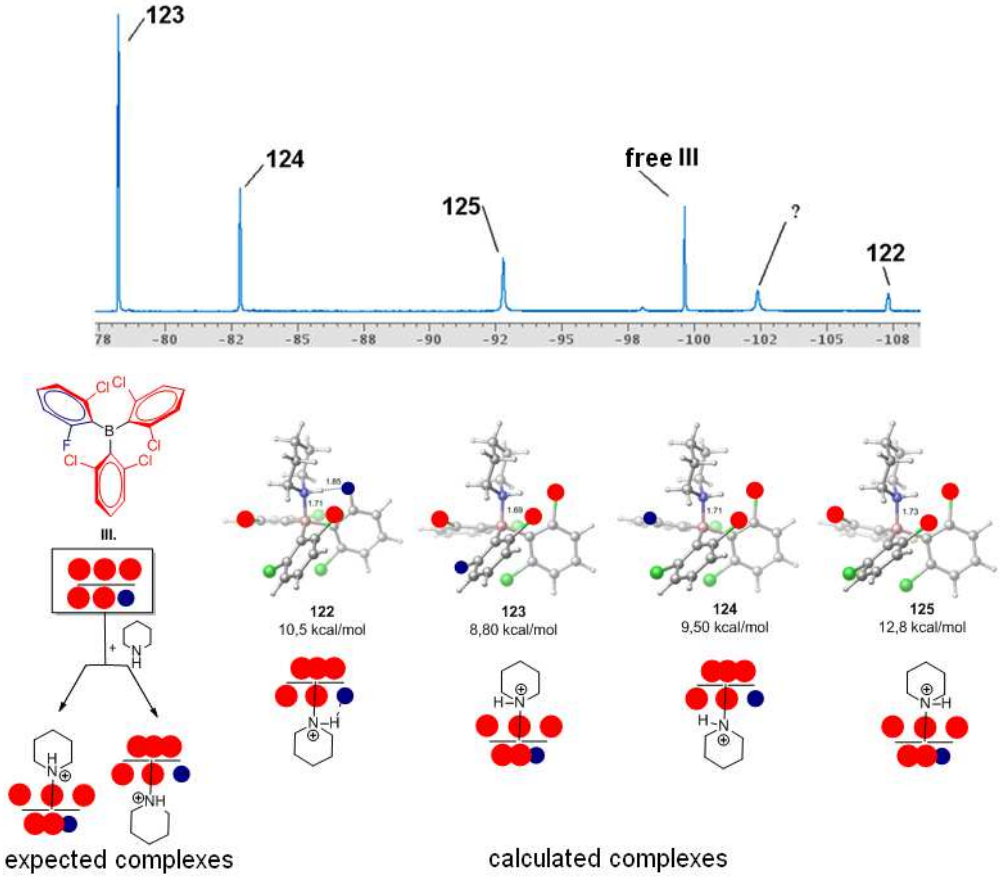
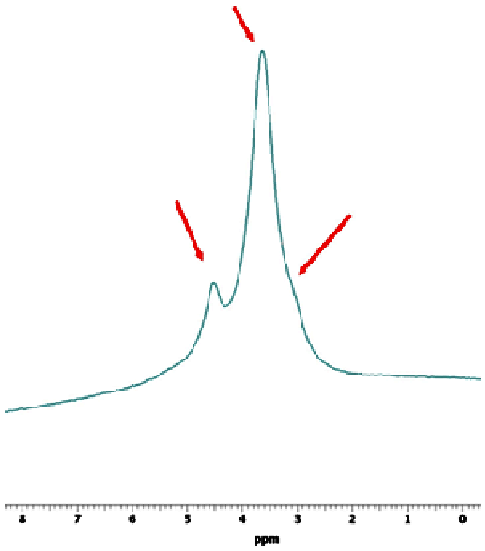
8. Complexes with different conformation were identified by using their non-systematically substituted borane III:piperidine complexes to perform low temperature ^{19}F NMR measurements and to carry out theoretical chemical calculations (Scheme 9.). According to the ^{10}B NMR spectra, in some dative complexes a slight difference can be discovered amidst the electron density of boron; that is the borane **III** has variable Lewis acidity strength (Scheme 10).

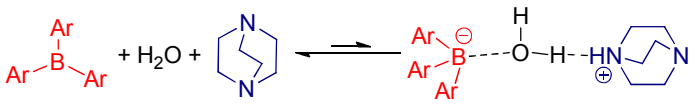


Scheme 9. The structure of the **III**-piperidine complexes by theoretical calculations..



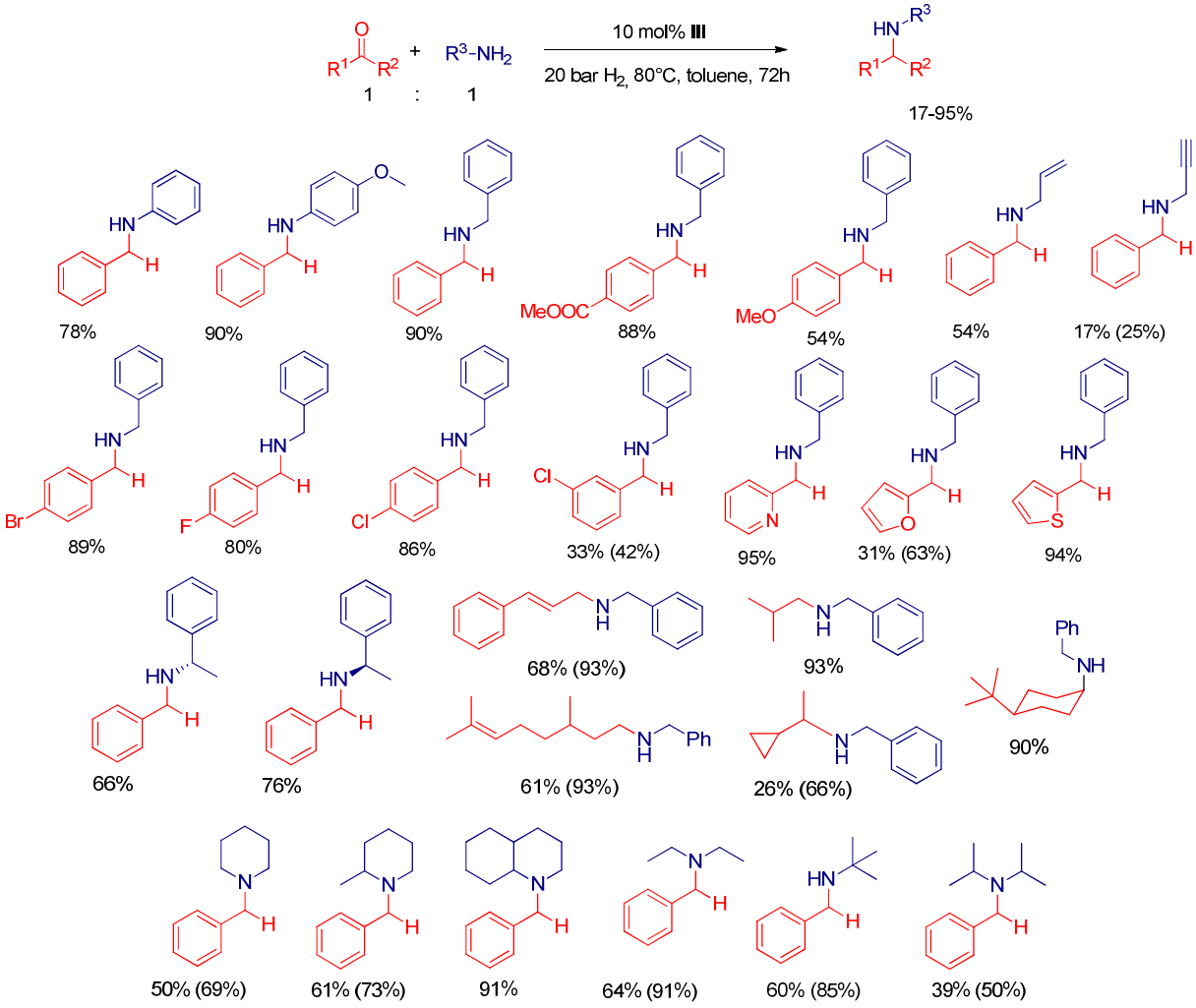
Scheme 10. The ^{10}B NMR spectra of the solution **III**:piperidine (1:3) at -30°C.

9. In the course of systematic fine-tuning it has been discovered that the back strain is an important element to consider when developing boron-nitrogen based FLP catalysts, especially to achieve water tolerance. Examining the behaviour of the non-symmetrically substituted boranes in the presence of water and DABCO base shows that the increased back strain of the Lewis acid weakens the formulating borane-water dative bond and makes it reversible (Scheme 11.).

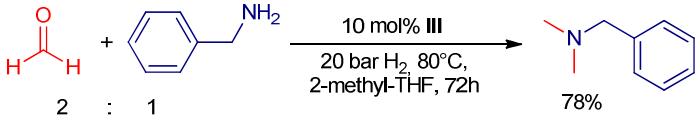


Scheme 11. The structure of the borane-water-DABCO complexes

10. Examining the reactivity related to the increased back strain we extended the chemical applicability of the FLPs. The benefits of the structurally fine-tuned Lewis acid **III** were demonstrated by reductive amination reactions of carbonyl compounds. These reactions are new methods in terms of FLP chemistry; they have a wild range of chemo-selectivity and can be generally used as metal-free processes (Scheme 12.). The double methylation of benzyl-amine with 37% water solution of formaldehyde was also performed in presence of 60 equiv. water due to the quantity of the catalyst (Scheme 13.).



Scheme 12. Reduction of carbonyl compounds with isolated yields and (conversions)



Scheme 13. Reduction of benzyl-amine with 37% formaldehyde solution

4. References

[1] Welch, G. C., San Juan, R. R.,Masuda, J. D., Stephan, D.W.,*Science,* **2006**, *314*, 1124.

[2] (a) Stephan, D. W.,Greenberg, S., Graham, T. W.,Chase, P., Hastie, J. J.,Geier, S. J.,Farrell, J. M., Brown, C. C.,Heiden, Z. M., Welch, G. C., Ullrich, M., *Inorg. Chem.*,**2011,***50*, 12338.; (b) Stephan, D. W., *Org. Biomol. Chem.*,**2012**, *10*, 5740.; (c) Stephan, D. W., Erker, G. *Angew.*,*Chem. Int. Ed.*,**2010**, *49*, 46.

Papers Forming the Basis of the Dissertation

„Correlating electronic and catalytic properties of frustrated Lewis pairs for imine hydrogenation”
É. Dorkó, B. Kótai, T. Földes, Á. Gyömöre, I. Pápai, T. Soós, *J. Organomet. Chem*., **2017**, *847*, 258-262. DOI: 10.1016/j.jorganchem.2017.04.031

„Expanding the Boundaries of Water-Tolerant Frustrated Lewis Pair Hydrogenation: Enhanced Back Strain in the Lewis Acid Enables the Reductive Amination of Carbonyls”
É. Dorkó, M. Szabó, B. Kótai, I. Pápai, A. Domján, T. Soós, *Angew. Chem. Int. Ed*. **2017**, *56*, 9512 –9516. DOI: 10.1002/anie.201703591